The Nose: Olfaction

Introduction

Olfaction is the sense of smell. Much like the other special senses, some external signal is translated and incorporated into an electrical signal that our brains can perceive. For olfaction, the signal is a chemical one—odorant molecules activate odorant receptors, then a cascade of neurons encodes the electrical impulses, and off to the brain the signal goes. Human evolution has taken smell from a survival instinct and transformed it into an aid to the brocavore's dining pleasure or the oenophile's discernment of a great vintage.

Olfaction is the translation of a chemical signal—**olfactory** receptors responding to an **odorant molecule**—into an electrical signal. That concept isn't new; we've seen such a system in nociceptors and taste buds. We've seen bipolar neurons in the function of vision, audition, and balance. And so olfaction is essentially, *"everything you've already learned, but in a different context."* You've been through a barrage of facts, each time having to learn a new, complex, and unrelated physiology throughout the Special Senses island. We end with a breather—a short lesson that recycles knowledge you've already gleaned from the rest of this island.

Olfaction Epithelium and Odor History

Perception of odors involves **bipolar neurons** within a **modified respiratory epithelium** located superior to the superior turbinate. In that modified epithelium, the **olfactory epithelium**, there are ciliated columnar cells, basal cells that act as stem cells, and mucin-secreting submucosal glands. That describes respiratory epithelium as well (olfactory epithelium and respiratory epithelium of the nasal cavity are contiguous with one another, share a common basement membrane, and have similarly shaped cells). The difference in histology (the cellular makeup of the epithelium) is that, in the olfactory epithelium, there are **bipolar neurons** and **no goblet cells.** Bipolar neurons wedge themselves between the ciliated columnar cells. The nucleus of the bipolar neuron is near the middle of the columnar cells' height. The bipolar neuron extends its dendritic arm to the apical surface of the ciliated columnar cells and its axon to the **cribriform plate** and onto nuclei within the **olfactory bulb**, which is within the cranial cavity.

The olfactory epithelium is located high in the nasal cavity. Olfactory receptors continually die, regenerate, and grow in a cycle that lasts approximately 4–8 weeks. Olfactory receptor cells are one of the very few **types of neurons** that are **regularly replaced throughout life**. This doesn't make logical sense to us, as the neurons of the nasal epithelium would have to continually regrow the correct synaptic connection with the olfactory bulb. Yet this is currently believed to be true. We're saying it because it is what is believed, although we are skeptical that it is truly the case. However, a high-speed head-on collision (not of cars but of the face to something else) could sever the connection between the olfactory neurons and the olfactory bulb via fracture of the sphenoid bone. Recovery of olfaction after trauma-induced anosmia has been documented. Recovery is variable. The fact that it can recover suggests that bipolar neurons are indeed being continuously turned over, just like epithelial cells.

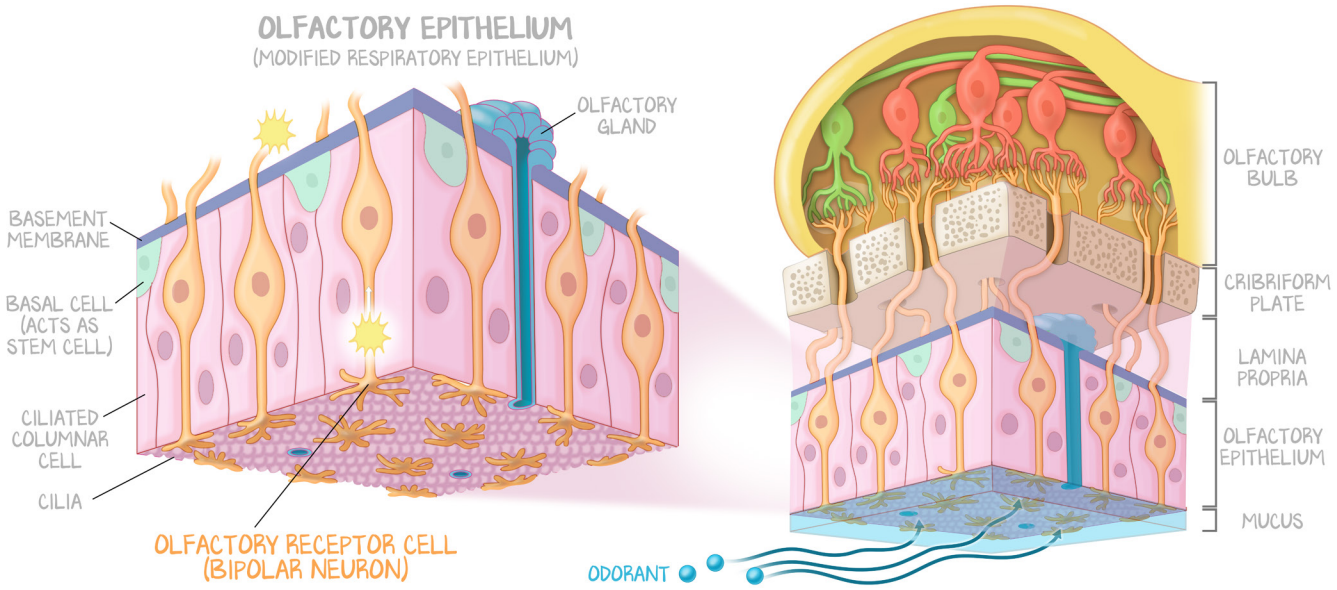

Figure 5.1: Olfactory Epithelium
The olfactory epithelium is a modified respiratory epithelium. There are olfactory glands (submucosal glands that secrete mucus) and simple columnar cells (just like respiratory epithelium), but instead of goblet cells, there are bipolar neurons with odorant receptors. These bipolar neurons project their axons through the cribriform plate and into the olfactory bulb, where they synapse on the cells whose axons will make up the olfactory nerve (technically, it is a tract, but it's often called nerve).

Olfaction is certainly more evolutionarily ancient than the other senses. The olfactory nerve and subsequent olfactory tract project axons to the deep brain, innervating the centers associated with pleasure and fear and other nebulous areas of the "limbic system." Olfaction is one of the elusive "midbrain functions" that every human experiences, but the mechanism of which medical science has yet to elucidate.

Over 40,000 **odorants**—molecules that can activate smell receptors—have been discovered, but only over 400 **odorant receptors** have been identified. That means that individual odorants activate different odorant receptors to different extents. And, like the sensation of general touch, the perception of smell is an aggregation of inputs. Of the 40,000 odorants, 80% are noxious (bad-smelling). This actually makes sense. An organism, far lower than humans, encounters a thing. It cannot see or hear the thing. It wonders if it should ingest that thing as food. Aside from simply eating the thing, the best indicator that it is safe to eat is its smell. Humans' use of smell has evolved away from a protective mechanism of survival instinct and shifted into one of behavior and reward, having embraced the purposeful ingestion of products made from fermented grains and roots (various alcohols), and even lutefisk.

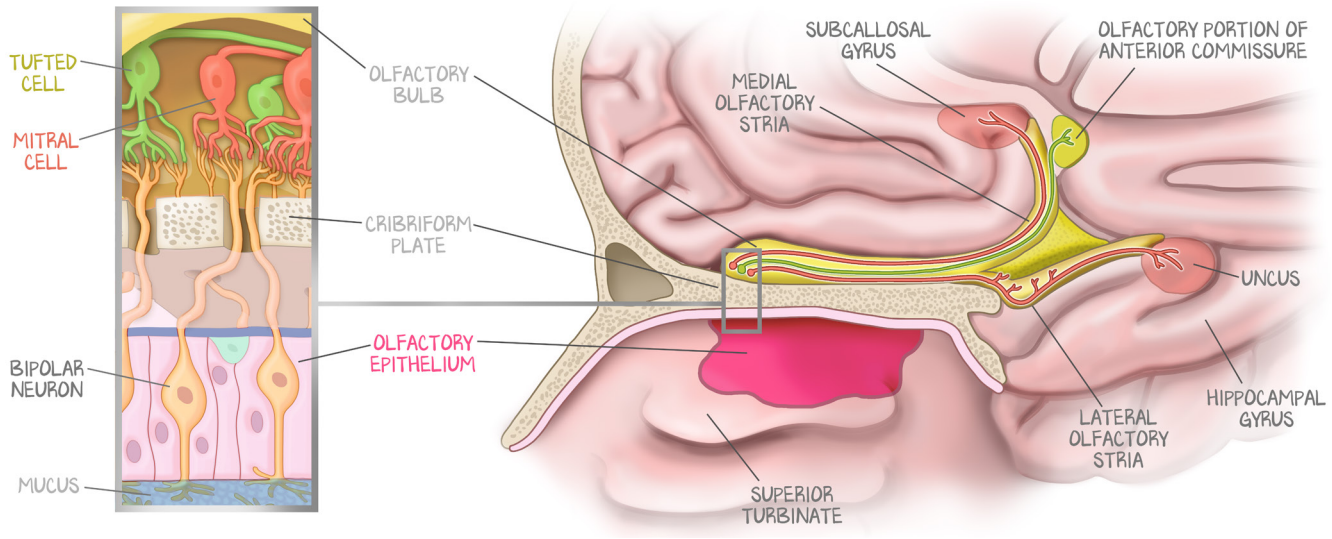

Figure 5.2: Olfactory Histology and Anatomy
The bipolar neurons project their axons through the cribriform plate and into spherical structures called glomeruli. Within the glomeruli, there are thousands of dendrites from the tufted cells and mitral cells above. Each tufted cell or mitral cell has many dendrites in multiple glomeruli. This illustration emphasizes how the olfactory bulb is the site of neuron cell bodies, and those neurons' axons project primarily to the deep brain. Some fibers synapse on the thalamus, which then transmits signals to the cortex (how humans perceive smell), but most go to evolutionarily older structures, particularly those of reward and emotion. Rather than trying to depict an accurate ratio of bipolar neurons to tufted/mitral cells, we wanted to give you the gist—bipolar neurons project to tufted/mitral cells, and those cells' axons project to the brain. This is the simplest of the special senses—only a bipolar neuron and the cell with the axon that projects to the cortex.

In the 1990s, Budweiser ran commercials about "bitter beer face," an indication that bitter beer was good beer gone bad. Back then, everyone agreed. Now, brewmasters rate their craft beers by how "hoppy" they are. Hoppy is just another word for bitter. It isn't as if humans' sense of smell has evolved in a single generation to somehow enjoy a foul taste. And yet now, hoppy beer has become popular. Budweiser beer gone bad is a bitter beer that offers offense to the consumer. The hoppiest beer, a bitter beer, is a drink of high privilege. Offer it to a lemur, and you'll likely get poo flung in your face—it smells dangerous, unsafe, and gross. The animal reacts to the smell with instinct. But rather than respond to our initial smell sensors, we are able to convince ourselves that foul-smelling beverages are indeed delicious. That's likely because the axons of olfaction primarily project to the brainstem and are integrated with the limbic system. Smell informs pleasure and behavior. Only a few of the axons end up in the cortex.

Odorant Physiology

The **submucosal glands** secrete an air-surface layer very similar to the **mucus** of the respiratory epithelium. And like the respiratory epithelium, the mucus creates a physical barrier, under which is an aqueous environment above the epithelium in the periciliary space. In order for an odorant molecule to find its receptor on the bipolar neuron, it must cross the mucus layer, then be escorted through the aqueous layer to the neuron dendrites where the receptors are. The simple columnar epithelium of the olfactory epithelium releases **odorant-binding proteins** into the periciliary aqueous environment. Odorants are usually lipophilic; they diffuse through the mucus layer, are stabilized by the odorant-binding protein, and are then brought to the bipolar cells, where the dendritic projections of the **bipolar neurons** have their odorant receptors.

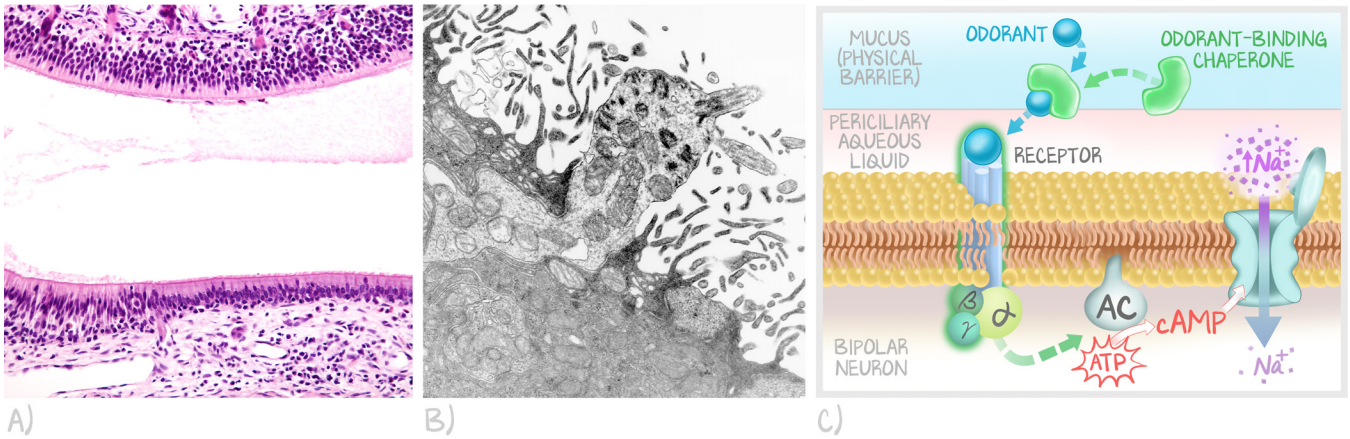

Figure 5.3: Odorant Physiology
(a) Transition from simple columnar epithelium (bottom right to just left of center) to olfactory epithelium (bottom left). The olfactory epithelium is definitely different (taller cells), but the stroma below looks identical. At the top of the image, there is only olfactory epithelium. Both epithelia are ciliated and secrete mucus. (b) Electron microscopy of a bipolar cell rising from the ciliated columnar cells around it. The odorant receptors project into the mucus for better access to odorants. (c) Lipophilic odorant molecules bind to chaperones to travel through the aqueous periciliary fluid and activate G_s-associated GPCRs, leading to the depolarization of the bipolar cell.

Odorant-binding proteins on bipolar neurons in the mucus probably facilitate the diffusion of odorants toward and away from the receptors. Other enzymes (poorly characterized) may help clear the mucus of odorants and thus the longer the organism remains in the presence of the odorant, the less severe it becomes. And that adaptation is fast. It may still be unpleasant, but few odors are severe enough to fail to dissipate.

Second Messengers

Odorant receptors are GPCRs. And some aspiring scientist can likely be cited (even awarded) for their pleasure in forcing the rest of us to endure a GPCR of the olfactory system that has the same physiology and outcome as one of the GPCRs you know well—one that uses G_s and operates through adenylyl cyclase and increased levels of cAMP—but is named Golf. Yes, Golf. Good one. You win, I'm jelly you thought of it first, but disappointed that medical science continues to use it. $G_{olfactory}$ is cleverly abbreviated G_{olf}. But what is golf? It is a game where you whack balls onto the grass and then into tiny holes if you're good and into the woods or a lake if you aren't. Oh, wait . . . actually, it's a trimeric G protein with an α-subunit that stimulates adenylyl cyclase. We already have a GPCR mechanism that INCREASES cAMP. It's called G_s. So Golf (no subscript, let's call it like it is) is a G_s, and increased levels of cAMP open ion channels. We won't look up who called it G_{olf}, and we are hoping that a second-year Ph.D. candidate purposefully transcribed it as Golf to get back at their review board. It's unlikely, and we are probably more cavalier than we should be . . . but . . . Golf?

cAMP is responsible for **opening nonspecific cation channels**, enabling calcium and sodium into the cell, leading to depolarization. In this sense, "chemoreception" is just the conversion of a chemical signal into an electrical signal, carried out by GPCRs. The bipolar neurons cells' axons project into the cranial cavity through the cribriform plate.

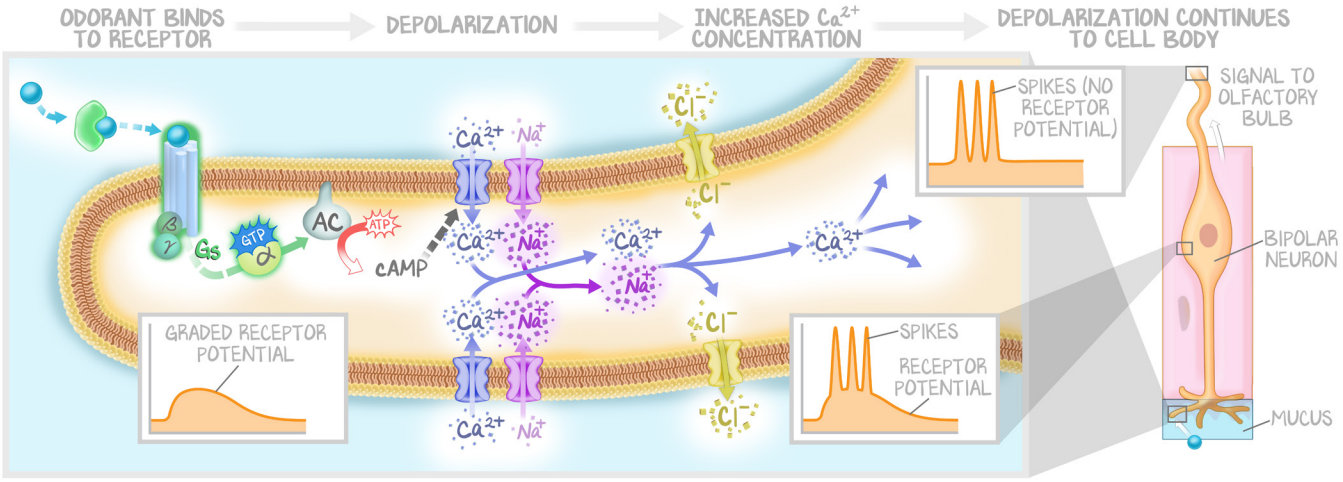

Figure 5.4: Bipolar Cells Encode Smell
Odorants act through G_s, increasing the amount of cAMP and, in turn, opening cAMP-dependent cation channels that enable sodium and calcium to enter the cytoplasm, depolarizing the membrane. This depolarizing effect is graded; it does not generate an action potential in the dendritic processes. Rather, the graded signal alters the frequency with which the bipolar neuron generates action potentials, projecting onto neurons in the olfactory bulb.

Twenty-five thousand bipolar axons project through the **cribriform plate** and onto globular dendritic structures within the **olfactory bulb** called glomeruli (which have nothing to do with and look nothing like kidney glomeruli). Each of these globular structures is the location of the dendrites of neurons with axons that project back towards the brainstem. Each globular structure has dendrites from 25 mitral cells and 60 tufted neurons, their cell bodies above the globular structure to which they belong. These cells form the final output to the brainstem. There are multiple projections, two of which never leave the brainstem and are highly correlated to the limbic system, which controls emotion, pleasure, and regulation of basic behavior, including the induction of salivation, licking the lips, and other feeding responses. Evolutionarily newer tracts pass through the thalamus on their way towards the cortex and enable our perception of smell.

Citations

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